National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Dapagliflozin in combination therapy for the treatment of type 2 diabetes

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, *7th December 2012* using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 2 (section 1.2) it is stated that ”The rates of bladder, prostate, and breast cancer were higher in the dapagliflozin group compared with placebo/comparators (with wide confidence intervals for the incidence rate ratios)“	“While the overall rates of malignancies detected in the trial programme were balanced across the dapagliflozin and comparator arms, the rates of bladder, prostate and breast cancer were numerically higher for the dapagliflozin arm compared with placebo/comparator (with wide confidence intervals for the incidence ratios)”	This puts the statement in a more balanced perspective	The suggested change is acceptable, but not necessary.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 2 (section 1.2) it states that ”There is a concern that the rates of bladder and breast cancer within the dapagliflozin programme are higher than those expected in the general T2DM population”	Please remove the statement	This statement is misleading. There is little firm evidence for actual rates of events in the type 2 diabetes population. In a trial where active urine testing was performed and the possibility of a detection bias, the absolute numbers were always going to be higher. The same would apply to breast cancer where weight loss would contribute to a detection bias.	The statement is correct and in line with the FDA position. What we are saying here is that there is a concern, not that the rates are proven to be higher.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 2 (section 1.2): regarding the analysis of malignancy, it is stated that "the total number of clinical trials which contributed to these rates was not given"	This information was provided at the clarification stage. However, the details are as follows: This is based on 19 Phase 2b/3 studies (list below if required again) Monotherapy=NCT00528372 Low dose monotherapy = NCT00736879 Monotherapy Phase 2=NCT00263276 Monotherapy (Japan)=NCT00972244 Add-on to MET=NCT00528879 With MET-XR (DAPA 5 mg)=NCT00643851 With MET-XR (DAPA 10 mg)=NCT00859898 DXA body composition=NCT00855166 Add-on to SU=NCT00680745 Add-on to PIO=NCT00683878 Add-on to insulin=NCT00673231 Add-on to insulin Phase 2b=NCT00357370 Add-on to MET vs SU=NCT00660907 Moderate renal impairment=NCT00663260 Patients with HT + CVD=NCT01031680 Patients with CVD=NCT01042977 Add-on to DPP-IV inhibitor=NCT00984867 Effect on GFR=NCT00976495 Insulin sensitivity=NCT00831779	The statement is untrue	We accept that this list of studies was given in the manufacturer's response, but there is a lack of detailed information about the inclusion criteria for these studies, their sample size and, more importantly, how many cancer cases were found in each study.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 2 (section 1.3) it states "very low cost of SUs and their	Remove the "known safety record"	SUs have a known record for increasing hypoglycaemia, are	This statement is not based only on cost. The safety

known safety record ..."		associated with an increase in cardiovascular events. So this statement is only based on cost.	record of the SUs is well-known because they have been around for decades and been studied in very large long-term trials such as UKPDS. The fact they can cause hypoglycaemia, is not in doubt - we know that from the aforesaid safety record. It is worth noting that recent data on the risk of hypoglycaemia is available from the ORIGIN trial, the standard care arm of which included 1810 pts on SU followed for mean of 6.2 years. In the standard arm, 25% were on SU. Hypoglycaemia was confirmed in 14% of patients in the standard arm. As a recent review noted, "ORIGIN may help us debunk the myth of sulfonylurea induced hypoglycaemia"…."even if we assume that all confirmed hypoglycemic episodes occurred in those using SUs, 30% would have been event free for the whole duration of the study,

			and less than 10% would experience a severe hypo event." (Diapedia, accessed 14/11/2102). The BMZ/AS comment gives no reference for the allegation about cardiovascular events.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 2 (section 1.3), bullet point 3, the following is incorrect: "Given the **absence** of head-to-head trials between dapagliflozin and active comparators…"	"Given the absence of head to head trials between dapagliflozin and **some** of the active comparators…"	Currently the sentence reads as though there are no comparative trials, whereas there is a relevant trial vs one of the comparators (i.e.SU) listed in the NICE STA scope.	The ERG does not regard SUs as comparators, but rather as precursors that would be tried first. Please change paragraph as follows: "Given the absence of head-to-head trials comparing dapagliflozin with other relevant comparators…"

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 (section 1.4) "The manufacturer used the dapagliflozin cost effectiveness model (DCEM), written in software not approved by NICE, with which the ERG was not familiar. Some of the usual checks could therefore not be carried out."	"The manufacturer used the dapagliflozin cost effectiveness model (DCEM), where the overall simulation was programmed in C++ also used in the CORE diabetes model previously reviewed by NICE."	The model language used in the dapagliflozin CE model is the same as used by the CORE model previously reviewed by NICE. The statement has significant impact in that it undermines the credibility of the model approach used for both the dapagliflozin model and the CORE model already reviewed by NICE.	The suggested amendment is misleading. The CORE model was accepted by NICE, with the consent of the Assessment Group (NB not ERG) involved, for an appraisal of insulin pumps. The longer time scale of that "MTA" style appraisal (though that term was not in use then) allowed the Assessment Group time to become familiar with CORE, aided by the large volume of published studies that had used CORE. The AG also obtained input from an expert in CORE. CORE has since then been accepted for other appraisals but only by ERG members who were involved in the insulin pumps appraisal. There are problems with CORE which also does not meet the NICE rules on software acceptability.

			However, the much shorter timescale of an STA does not allow an ERG to become familiar with a new model written in unapproved software. ERGs cannot be expected to be familiar with every possible software on the market, which is why NICE adopted the short-list of approved software. The statement is correct and will not be changed.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19 (section 3.2) it is stated that ”In April 2012, the CHMP issued a recommendation that dapagliflozin should be approved”	“Marketing authorisation was granted in November 2012”	Marketing authorisation was granted in November 2012	Accepted, but that was not known at the time the ERG report was written. The EMEA website was checked early November.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 22 (section 4.1.1), it states, “Furthermore, no	This is incorrect. Two reports from Oxford Outcomes were provided which updated	Incorrect statement.	The ERG did not have the time to go in details through

systematic searching was undertaken after May 2011."	the literature searches to June 2012: these were sent to NICE in the company reference pack in July 2012		the large reference pack sent by the manufacturer. For clarity and transparency, this information should have been presented in the main text. Please note that the current submission was 284 pages long (without references) and more than 100 pages of Appendices.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 22 (section 4.1.1), regarding three of the five main dapagliflozin RCTs, it states that "it is unclear which methods were used to identify these additional papers."	"Methods for identifying papers associated with included dapagliflozin RCTs that were included after the search date were clear."	In section 9.2.3 of the submission, it states that "Unpublished trials in the BMS/AZ dapagliflozin clinical trial program were searched by reviewing a list of all on-going and completed RCTs, provided by the manufacturer". These trials were unpublished at the time of the search execution, but met inclusion criteria. Published data were available prior to submission and therefore the submission was updated to reference these publications.	Section 9.2.3 (in Appendix 2 of the submission) lists the additional sources searched by the manufacturer (conference proceedings, clinical databases, etc). However, it is unclear how many abstracts/records were initially screened, how many were selected (from which sources) because potentially relevant and how many were ultimately included in the current submission.

			This information should have been clearly reported in the main text of the submission.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25 (section 4.1.4) it is stated that ”The ERG did, however, have concerns about the sensitivity of the literature search and the fact that it appeared that the search had not been updated since May 2011”	“An update was carried out in 2012, updating the searches to 4 June 2012”	Incorrect statement.	Appendix 2 of the submission, which gives details of the search strategies performed by the manufacturer, reports May 2011 as the search date. Therefore, it is unclear whether an update of the search was formally performed.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 37 (, the ERG states “*Although results are also provided for DPP4 and after including the TZD trial, the ERG considers the reporting of this section of the manufacturer’s submission (p.132) rather*	*“Results were also provided for DPP4 (relative effect between dapagliflozin and DPP4 was -0.14 (-0.34, 0.07)), and TZD. For the latter comparison, the relative effect size was considered to be affected by the high baseline HbA1c in the RCT involving TZD (9.8%)."*	Without this amendment, the relative effect size for dapagliflozin vs. DPP4 is not presented.	The ERG still believes the results shown on pages 131-133 to be confusing. Although TZD is excluded from the main analysis, the result for DPP-4 versus placebo appears in a sentence also giving results

unclear."			for TZD. The ERG therefore found it unclear whether or not the results for DPP-4 versus placebo were derived from a network which includes TZD.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 40 (section 4.3.1), "It is not clear whether studies with a duration between 30 and 46 weeks or greater than 58 weeks were also identified."	"It is not made explicit whether studies with a duration between 31 and 45 weeks (inclusive) or greater than 58 weeks were also identified; however a full listing of identified RCTs was provided, and among those no RCTs durations were between 31 and 45 weeks. Interim data from RCTs of greater than 58 weeks were included where available, and a description of interim data that were included and excluded is provided in section 5.7.5 ("Inclusion of interim data")."	Clarification required to confirm that no potentially informative data were omitted.	We accept the manufacturer's comment. However, we would like to stress the point that it was not easy to locate the relevant information in the BMS/AZ submission and, as only one time point is given for each study, it is still not clear if there are studies with interim time points that are between 31 and 45 weeks.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42 (section 4.3.1), it states, "In the main text they presented a mixture of adjusted and unadjusted	"In the main text they presented a mixture of adjusted and unadjusted results. They explained that the a priori choice of model was a random effects model adjusted for	The recommended changes are pulled directly from the submission, section 5.7.5,	The ERG still believes the decision making process used to select adjusted or unadjusted models to lack

results and explained that the decision was based on the a priori choice of model (i.e. a random effects model adjusted for baseline HbA1c), statistical and clinical significance of the model coefficient, the model fit and assessment of the posterior distribution of the between studies variance. In the footnote to Tables 25 and 26 of the manufacturer's submission, it is also stated that a model whose deviance information criterion (DIC) is at least three points lower than that of another model is deemed to have better fit, but it is difficult to reconcile this with the DIC values given in these tables."	baseline HbA1c, but stated that a fixed effect model would be selected if it offered better fit (referencing Spiegelhalter et al 2002, who recommends that a deviance information criterion (DIC) at least three points lower than that of another model indicates better model fit. They further specified that the posterior distribution of the between studies standard deviation was investigated to ensure that it was updated from the prior distribution based on the available evidence and that where the prior distribution dominated, the fixed effect model was selected. Selection between adjusted and unadjusted models was selected to promote parsimony, and the adjusted model (based on the covariate*treatment interaction term) was selected based on: a) model fit, b) statistical significance of coefficient, and c) clinically meaningful effect size."	subsection "Model selection".	transparency and reproducibility. The process used to select models using the three criteria (a-c) the manufacturer describes is not made clear in the submission. In particular, although some DIC values are presented in Tables 25 and 26, it is unclear whether the choice of model was based on these or on other factors.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42 (section 4.3.2), it states, "The drugs and doses for the insulin add-on NMA do not seem to be given explicitly."	"The drugs and doses for the insulin add-on NMA were not provided in section 5, but were provided in Appendix 16 (9.16; Table 112), and included sitagliptin 100mg, saxagliptin 5mg, pioglitazone 30mg, and dapagliflozin 10mg."	These data are critical for the interpretation of the results of the insulin network.	The data were not given in the main text of the submission. NICE guidance to manufacturers is that submissions should be around 100 pages long.

			ERGs cannot be held responsible for finding details buried in appendices. The NICE guidance to manufacturer states that "Appendices should not be used for core information". If as BMS/AZ says, "These data are critical", they should have been presented in the main text. There were 19 appendices (more than 100 pages) in the BMS/AZ submission. The main submission was 283 pages long, not counting references, though about 50 pages are from the NICE template text.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 44 (section 4.3.3) it is stated that "No up-to-date searches were performed and only studies involving some kinds of triple therapy were included"	Trials since 2009 that resulted in OADS getting a triple therapy license were added (saxagliptin and linagliptin)	The ERG accepts that DPP4s were the relevant comparator in this space so the relevant studies were included. As their result did not differ from the 2009 MTC, it was not expected that these would result in substantial changes to the MTC	The ERG accepts the proposed amendment.

		results.	

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 45 (section 4.3.4) it is stated that ”The ERG was concerned that there was a lack of transparency as to how studies had been selected for this analysis and that simple pooling had been used instead of formal meta-analysis techniques”	Suggest statement is removed	The method to select the trials was very simple. Essentially, every study was included in which a patient with type 2 diabetes was given at least one dose of dapagliflozin. There was no selection of studies beyond this criterion and this was the widest group available.	This statement should be retained. Different inclusion criteria are used for the main outcomes and for different types of adverse events and there is a lack of transparency about the inclusion criteria for each outcome.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 46 (section 4.5) it is stated that ”but since the SUs are old and cheap drugs with a known safety record, one would expect them to be tried before dapagliflozin”	Suggest “with a known safety record” is removed and amended to “but since the SUs established and inexpensive, one would expect...”	This statement seems to suggest SUs are safe: SUs are associated with hypoglycaemia and increase in rates of CV events. So we believe that the statement requires amending.	No change. The statement about known safety record is correct. It is about the record.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 104 (section 5.5). The text in this section is just a set of questions so we wonder if this is an error	This section should be omitted or interpretable text added.	The questions posed as they are have no meaning and serve no purpose	The ERG accepts the proposed amendment (please delete the paragraph).

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 107 (section 7, under 'Summary of cost-effectiveness issues), "It may be most cost effective to try a **safe** cheap drug first and check whether there is a sufficient response before trying a new more expensive drug"	Remove the word 'safe'.	It is incorrect to use the word 'safe', as all drugs are associated with some side effects.	Please change paragraph as follows: It may be most cost effective to try a cheap drug **with a known safety record** first and check whether there is a sufficient response before trying a new more expensive drug.